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09/578,224	05/24/2000	Thomas Schwalbe	CELL0013	4618

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EXAMINER	
LEUNG, JENNIFER A	
ART UNIT	**PAPER NUMBER**
1764	

DATE MAILED: 04/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/578,224	SCHWALBE ET AL.	
	Examiner	Art Unit	
	Jennifer A. Leung	1764	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14,16-24,26 and 71-77* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14,16-24,26 and 71-77* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *01/12/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 12, 2004 has been entered.

Response to Amendment

2. Applicant's amendment submitted on January 12, 2004 has been received and carefully considered. Claims 15, 25 and 27-70 are cancelled. Claims 75-77 are newly added. Claims 1-14, 16-24, 26 and 71-77 remain active.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 1-5, 9-14, 18, 20-24, 26 and 71-74 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bard (US 5,580,523) in view of Manz (US 5,250,263) and Agrafiotis et al. (US 5,463,564).

Regarding claims 1 and 71, Bard (FIG. 2, 3, 4; generally, column 4, lines 21 - column 5, line 18 and column 6, line 66 - column 7, line 20) discloses a modular system for synthesizing a variety of chemical products, comprising:

(a) a control module, adapted to monitor and automatically control the production of a chemical product (i.e., interface **90** communicating with master control center or computer -- inherently a processor. Note that reference **90** is unlabeled in FIG. 4);

(b) a reactant supply source **A**, **B** for a plurality of reactants (FIG. 4), a flow of each reactant being controlled by the control module; and

(c) a first reaction module in fluid communication with reactant supply sources **A**, **B**, wherein the first reaction module is controllably connected to the control module and comprises a replaceable reactor **R** (i.e. configured as a detachable and interchangeable reaction chip type unit; column 2, lines 32-47; column 4, lines 53-64), wherein reactor **R** produces the chemical product from reactants **A**, **B** under control of the control module.

Bard discloses the "chip-type" replaceable reactor **R** comprises an etched substrate **1** defining a plurality of fluid pathways **10**, **11** and a reaction volume **4** (FIG. 1a-1d), wherein multiple photolithographic processes may be necessary if more complex structures are desired, (column 5, lines 18-48). However, Bard is silent as to whether replaceable reactor **R** may comprise, specifically, a plurality of simple plates (i.e., instead of a single etched substrate **1**), wherein the simple plates are configured such that aligned openings in the plurality of plates define at least

two reactant fluid pathways, at least one reaction volume, and at least one product fluid pathway.

Manz teaches an alternate "chip-type" reactor **1** (i.e., FIG. 4, 5, 14a-h to 16; column 3, lines 34-64) wherein the reactor **1** comprises a plurality of simple plates (i.e., "chip-like wafers" or plate-like components **8**), each plate **8** comprising a plurality of etched openings (i.e., openings **9**, **10**, **12**, etc.) that penetrate through a first and a second planar surface, but not an edge surface, of each plate **8**, wherein the plates **8** are configured such that the openings, when aligned, define at least two reactant fluid pathways and at least one product fluid pathway (i.e., as defined by pipe parts **9**, flow openings **10**) in fluid communication with at least one reaction volume (i.e., as defined by central chambers **12**).

It would have been obvious for one of ordinary skill in the art at the time the invention was made to substitute a "chip-type" reactor **1** as taught by Manz for the "chip-type" reactor **R** in the apparatus of Bard, on the basis of suitability for the intended use, because the substitution of known equivalent structures involves only ordinary skill in the art. *In re Fout* 213 USPQ 532 (CCPA 1982); *In re Susi* 169 USPQ 423 (CCPA 1971); *In re Siebentritt* 152 USPQ 618 (CCPA 1967); *In re Ruff* 118 USPQ 343 (CCPA 1958). Furthermore, Manz (column 2, lines 3-10 and 46-57) teaches that by configuring the reactor **1** as a plurality of simple plates **8**,

> "[s]uch plate-like components can be miniaturized relatively easily and permit an important development of the invention to the effect that the components can be stacked in varying number and/or sequence and/or orientation relative to one another to construct different flow systems and flow pipes and, in the operative position, are connected in a sealing manner," and
>
> "[t]he connection of the apparatus to a control device can be effected in a simple manner via electrical cables... via hydraulic and/or pneumatic hoses... or via feed hoses... this is rendered possible by the stacking according to the invention of plate-like components having corresponding openings and channel sections, so that the entire apparatus may be in such a form that it is very space-saving and has a small inherent volume."

The collective teachings of Bard and Manz are silent as to the control module comprising a reaction database, such that a user may interact with interface **90** to select a specific reaction to produce the chemical product from a plurality of reactions stored in the reaction database.

Agrafiotis et al. (FIG. 1, 2, 11) teaches a computer-based system for iteratively generating chemical entities utilizing apparatus such as the Chemical Synthesis Robot **112** (column 7, lines 34-44; column 8, line 22 to column 9, line 38), wherein the system includes a control module comprising a processor **106** (column 7, lines 48-55), a reaction database (for synthesizing the Directed Diversity Chemical Library **208** using stored Structure-Activity Data **210** and Historical Structure-Activity Data **212**; column 7, lines 5-27) and a user interface (input devices **121**; column 8, lines 7-14). The control module enables a user to interact via interface **121** to select a specific reaction to produce a desired chemical product (lead compound **216**) from a plurality of stored reactions, so that in response to a selection made by a user, the processor **106** automatically controls the Synthesis Robot **112** (via logic **108**) to produce the product **216** according to the stored reaction parameters (synthesis instructions **204**).

It would have been obvious for one of ordinary skill in the art at the time the invention was made to provide a control module having a reaction database for the control module in the apparatus of Bard et al. because a reaction database provides a means for the storage of chemical property data from previously synthesized compounds, thereby enabling the iterative generation of directed, new synthesis instructions for controlling future chemical compound synthesis, as taught by Agrafiotis et al. (column 3, line 28 to column 4, line 16).

Regarding claims 2 and 73, Bard (FIG. 4; column 7, lines 1-20) discloses a mixer **Mx**, inherently defining a mixing volume, located upstream of reactor **R**. However, Bard is silent as

to whether the reactor **R** volume and the mixer **Mx** volume may be configured integrally such that reactor **R** comprises both mixing and reaction volumes. In any event, it would have been an obvious design choice for one of ordinary skill in the art to integrate both the mixing and reactor volumes on the replaceable reactor **R** in the modified apparatus of Bard, on the basis of suitability for the intended use, since the integration of parts merely involves ordinary skill in the art. To evidence conventionality, Manz teaches, "[o]ne plate-like component in each case can comprise at least one functional part of the apparatus, for example a valve, *a mixing chamber*, a pump element, extractors, *reactors*, connecting pieces and/or detector cells... Such functional parts can accordingly be incorporated and accommodated without difficulty at a required site within the stack of components," (column 2, lines 23-30). The integration of the plate-like functional parts of the apparatus minimizes the amount of reagents necessary and allows for shortened transport time (column 1, lines 46-65).

Regarding claim 3, Bard discloses the apparatus is particularly applicable for the synthesis of compounds under extreme conditions, such as supercritical temperatures and pressures (column 3, lines 24-30, 53-58). Supercritical fluids exhibit properties much like that of gases, and thus the apparatus is inherently capable of accommodating a gaseous reactant. Also, the chip-type reactors as taught by Manz are inherently capable of accommodating a gaseous reactant, as evidenced by the plate-like components defining sealed surfaces and edges at the flow openings (column 3, lines 53-65).

Regarding claim 4, Bard discloses a pump module (comprising pumps $\mathbf{P_A}$, $\mathbf{P_B}$) controllably connected to the control module (via signal **P**) and in fluid communication with each reactant supply source **A**, **B** and with said first reaction module, the pump module pumping

at least one fluid **A**, **B** through the modular system (FIG. 4; column 7, lines 9-20).

Regarding claims 5, 9, and 10, Bard discloses an additional processing module may be placed in fluid communication with the first reaction module and comprise a second reaction module, wherein the additional processing module is controllably connected to the control module and includes a reactor (i.e., a reactor **R**), so that the apparatus produces the chemical product using a plurality of synthesis steps, a first synthesis step being completed in the first reaction module and a second synthesis step being completed in the second reaction module. This reads on Bard's, "serial placement of reactors to allow controlled sequential reactions of intermediates," and "a plurality of individual, detachable reaction units," wherein, "one of the reaction units may be structurally different and capable of permitting a different chemical process of being performed," (column 2, lines 32-47 and 61-67; column 4, lines 53-58).

Regarding claim 11, Bard discloses reactor **R** configured for producing a class of chemical products (i.e., classes synthesized by either "thermal, electrochemical, catalytic, enzymatic, photochemical, or hollow chamber type" reactors; column 2, lines 32-47; column 4, lines 53-64), and is selectively readily removable from the first reaction module and replaceable with a different reactor **R** configured for production of a different class of chemical products.

Regarding claims 12 and 24, as modified by Manz, the replaceable reactor **R** of Bard now comprises a plurality of simple plates or plate-like components. Furthermore, the plate-like components may accommodate at least one functional part of the apparatus, for example a valve, a mixing chamber, a pump element, and reactors, without difficulty," (column 2, lines 23-30; column 2, lines 58-60). Manz teaches that in order to securely connect the individual plate-like components **8** to form a coherent stack **1**, a housing and mounting frame may be provided,

wherein the housing and frame comprise, "closing wafers **25** having connections as inlet **20** and outlet **21** to the flow channels of the apparatus" and "threaded rods or screws extending through the connecting or positioning holes **28** can be provided in a manner not shown in detail," (column 7, lines 4-26; column 8, lines 24-35; FIG. 11-13). It would have been obvious for one of ordinary skill in the art at the time the invention was made to provide a housing and mounting frame to the modified apparatus of Bard because such would enable the plurality of simple plates to be pressed together in a sealed manner, as taught by Manz.

Regarding claims 13 and 14, Bard (column 7, lines 1-20) discloses the first reaction module comprises means for facilitating production of the chemical product, wherein said means comprises a heat exchanger (a "heat transfer system" illustrated as **H** in FIG. 4, not labeled in the specification) and a temperature sensor (a thermocouple **TC**).

Regarding claim 18, Bard discloses the pump module comprises at least one pump $\mathbf{P_A}$, $\mathbf{P_B}$ controllably connected to the control module to control its operation (FIG. 4; column 4, lines 35-37; column 7, lines 9-20).

Regarding claims 20 and 21, Bard discloses at least one pump $\mathbf{P_A}$, $\mathbf{P_B}$ in fluid communication with both the reactant supply source and the first reaction module, wherein a separate pump is provided for each of the plurality of reactants **A**, **B** for communication with the first reaction module (pump $\mathbf{P_A}$ for source **A**; pump $\mathbf{P_B}$ for source **B**; FIG. 4).

Regarding claim 22, Bard discloses the pump module comprises at least one valve ($\mathbf{V_A}$, $\mathbf{V_B}$), being controllably connected to the control module (via signal **V**) to control a flow of reactants **A**, **B** to the first reaction module (FIG. 4; column 7, lines 9-20).

Regarding claim 23, Bard discloses the modular system may comprise separatory

components for performing a desired chemical process, and further illustrates the desired chemical process of penicillin fermentation, wherein the pump module comprises filter banks **502**, **503**, for filtering material from Benzylpenicillin (BP) before the BP flows to the reaction module (FIG. 8; column 4, lines 21-29, 46-52; column 6, lines 34-40; column 8, lines 35-67).

Regarding claim 26, Bard (FIG. 2, 3; column 4, lines 30-36; column 6, lines 26-33) discloses the modules may be fastened together for easy replacement and/or interchangeability using quick connect connectors (i.e. pins **30-37** or clips).

Regarding claims 72 and 74, Bard discloses the replaceable reactor **R** may comprise a microreactor (column 1, lines 7-10; column 3, lines 31-36).

2. Claims 6-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bard (U.S. 5,580,523) in view of Manz (US 5,250,263) and Agrafiotis et al. (U.S. 5,463,564), as applied to claims 1 and 5 above, and further in view of Ghosh et al. (U.S. 5,961,932).

Regarding claims 6 and 7, Bard discloses a chamber having an I.D. of up to 100 μm to optimize the control of *residence time* within a reaction zone, thereby comprising a "residence time module" (Abstract; column 3, lines 31-36). The chamber may be formed by etching a preformed pattern of a desired volume onto a substrate (column 5, lines 28-31; generally in lines 1-18), wherein the pattern inherently comprises a capillary, as characterized by its small internal diameter. Bard is silent as to whether the volume of the preformed pattern may be varied by selecting a capillary of a given length to obtain a predetermined amount of residence time for the chemical product. Ghosh et al. teach a chemical reactor comprising a chamber **34** which can be made longer by configuring serpentine, complex, wavy, winding and angular forms to allow for longer reaction time (column 5, lines 15-19). It would have been obvious for one of ordinary

skill in the art at the time the invention was made to modify the module of Bard such that it comprised a capillary of an appropriate length to obtain a predetermined residence time for the reaction, on the basis of suitability for the intended use, since such would allow for the reaction chamber to be designed specifically for a given reaction or reagent/product. Furthermore, it has been held that changes in size involve only ordinary skill in the art, and where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art.

Regarding claim 8, Bard discloses the, "system provides for uniform temperature control for continuous flow reactors under *elevated pressures*. This allows for precise control of *residence time* within a reaction zone." (column 2, lines 48-51). Bard further discloses, "flow control components that make-up the ICS system can include pumps, flow channels, manifolds, flow restrictor, *valves*, etc." (column 4, lines 36-37). Thus, it would have been obvious for one of ordinary skill in the art at the time the invention was made to supply a proportional valve to the residence time module in order to selectively vary pressure within the system of Bard, on the basis of suitability for the intended use, since such valves would be inherent of the apparatus (see also, column 3, lines 54-59).

3. Claims 16, 17 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bard (U.S. 5,580,523) in view of Manz (US 5,250,263) and Agrafiotis et al. (U.S. 5,463,564), as applied to claim 1 above, and further in view of Ashmead et al. (U.S. 5,534,328).

Bard (FIG. 1d, 3) discloses a plurality of fluid paths (channels **10**, **11**, **81**, **82**, **83**, **84**), including a fluid path for each of the plurality of reactants (reactants **A**, **B**, flowing into channels **81, 10**; also FIG. 4), and a fluid path for the product (intermediate products flowing through

channels **11** and **82** or **83**; final product flowing out of the modular system, via channels **11**, **84**). Bard further discloses a heat transfer system (illustrated as **H** in FIG. 4; column 7, lines 1-20). However, Bard is silent as to heat transfer system **H** comprising at least one fluid path for a heat transfer media and at least one fluid path for a spent heat transfer media configured as a parallel or serial fluidic system, wherein at least one pump is provided in fluid communication with both a heat transfer media fluid supply and the first reaction module. In any event, it would have been obvious for one of ordinary skill in the art at the time the invention was made to select such a configuration for the heat transfer system of Bard, on the basis of suitability for the intended use, since substitution of known equivalent structures involves only ordinary skill in the art. Such heat transfer systems (i.e. systems comprising flowing, fluid heat transfer media) are conventionally known in the art, as evidenced by Ashmead et al. (FIG. 3, 10; column 2, lines 4-17; column 11, line 66 to column 12, line 15) who teaches a reaction module comprising a heat exchanger **74**, wherein the heat exchanger comprises at least one fluid path for a heat transfer media (via inlet port **75** and flow channels **74C**) and at least one fluid path for a spent heat transfer media (via channels **74C** and outlet port **76**), wherein the fluid paths are configured in a parallel fluidic system (parallel channels **74C**, divided by **77-1**, **77-2**). Ashmead et al. further teach that external flow control means (not shown) may be used for controlling the temperature of the heat exchanger **74**, wherein such external flow control means may comprise a heat transfer media fluid supply (i.e. "a water bath") and known control devices, such as "pumps" (column 7, lines 28-47).

4. Claims 75-77 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bard (U.S. 5,580,523) in view of Manz (US 5,250,263).

Regarding claims 75 and 76, the same comments with respect to Bard and Manz apply (see claims 1 and 71 above).

Regarding claim 77, the same comments with respect to Bard and Manz apply (see claims 1 and 71 above). As modified by Manz, the replaceable reactor **R** of Bard now comprises a plurality of simple plates or plate-like components. Manz teaches that in order to securely connect the individual plate-like components **8** to form a coherent stack **1**, a housing and mounting frame in the form of, "closing wafers **25** having connections as inlet **20** and outlet **21** to the flow channels of the apparatus" and "threaded rods or screws extending through the connecting or positioning holes **28** can be provided in a manner not shown in detail," (column 7, lines 4-26; column 8, lines 24-35; FIG. 11-13). It would have been obvious for one of ordinary skill in the art at the time the invention was made to provide a housing and mounting frame to the modified apparatus of Bard because such would enable the plurality of simple plates to be pressed together in a sealed manner, as taught by Manz.

Response to Arguments

4. Applicant's arguments filed January 12, 2004 with respect to the rejection of claims 1-14, 16-24, 26 and 71-77 under 35 U.S.C. as being unpatentable over Bard, in view of secondary references, have been considered but are moot in view of the new grounds of rejection.

Conclusion

5. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure: Hartley is provided to illustrate the state of the art. Note the embodiment of FIG. 15, which illustrates a modular system comprising a plurality of reagent supply sources **170**, **171**, a plurality of micro-pumps **151**, and a combination micro-mixer/reactor **173**.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer A. Leung whose telephone number is (571) 272-1449. The examiner can normally be reached on 8:30 am - 5:30 pm M-F, every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Glenn A. Caldarola can be reached on (571) 272-1444. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jennifer A. Leung
April 13, 2004

Hien Tran

HIEN TRAN
PRIMARY EXAMINER